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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/063,597 | 05/03/2002 | Dan L. Eaton | P3230R1C001-168 | 2713 |

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KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

| EXAMINER | |
|---|---|
| WEGERT, SANDRA L | |
| ART UNIT | PAPER NUMBER |
| 1647 | |

DATE MAILED: 12/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/063,597 | EATON ET AL. | |
| | Examiner | Art Unit | |
| | Sandra Wegert | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## Detailed Action

***Status of Application, Amendments, and/or Claims***

In view of the papers filed 27 September 2004, the inventorship in this nonprovisional application has been changed by the deletion of: Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen and Colin K. Watanabe.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

The Amendment, submitted 27 September 2004, has been entered. Claim 1 is amended. Claim 6 is cancelled.

Claims 1-5 are under examination in the Instant Application.

The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior Office action.

## Withdrawn Objections And/or Rejections

***URL's***

The objection to the Specification because it contained browser-executable code, is *withdrawn.* Applicants amended the Specification to remove all URL's (27 September 2004).

***35 USC § 112, first paragraph – Deposit Rules***

The rejection of Claims 1-5 under 35 U.S.C. § 112, first paragraph, for not complying with the enablement requirement, is *withdrawn*. Applicants amended the Specification to insert language DNA66519-1535 guaranteeing unrestricted availability of the deposited nucleic acid molecules (clone).

***35 USC § 112, second paragraph***

The rejection of Claims 1 and 6 under 35 U.S.C. 112, second paragraph, for being indefinite is *withdrawn*. Applicants cancelled Claim 6 and amended Claim 1 such that it now recites "*specifically* binds" (27 September 2004).

**Maintained Objections and/or Rejections**

***Continuity***

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119. Applicants have argued that they are entitled to the benefit of at least Provisional Application 60/100,662. However, since the claimed invention does not have Utility, the Provisional patent applications listed, although disclosing the same experimental assays as the instant specification, do not impart Utility to the instant invention. Therefore, the filing date of 3 May 2002 is considered as the priority date.

***35 U.S.C. § 101/112, first paragraph-, Lack of Utility, Enablement.***

Claims 1-5 are rejected under 35 U.S.C. 101, as lacking utility. The reasons for this rejection under *35 U.S.C. § 101* are set forth at pp. 3-9 of the previous Office Action (30 June 2004). Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Action (30 June 2004), one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue (27 September 2004, pages 7 and 8) that the results presented in the instant Specification are enabling for the antibody that binds the polypeptide of SEQ ID NO: 90. They argue that the PRO1268 nucleic acid is a diagnostic marker for kidney tumors, and point to the results of the amplification assay which showed an approximately 2-fold amplification of the PRO1268 DNA in some kidney tumor tissue.

Applicant's arguments (27 September 2004) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the specification provides data showing a very small increase in DNA copy number- about 2 fold- in some kidney tumors. However, there is no evidence regarding whether or not PRO1268 mRNA or polypeptide levels are also increased in these cancers. Furthermore, as discussed in the previous Office Action (22 March 2004, pages 4 and 5), what is often seen is a *lack* of correlation between DNA amplification and increased peptide levels (Pennica, et al, 1998, Proc. Natl. Acad. Sci., 95: 14717-14722). As discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to the results presented, the ratio varies from zero to 50-fold

(page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2: 405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Given the small increase in DNA copy number of PRO1268, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a small increase in gene copy number, in both normal tissues and cancer tissues, would correlate with significantly increased mRNA or polypeptide levels. Further research needs to be done to determine whether the small increase in PRO1268 DNA supports a role for the antibody in detecting or treating cancerous tissue; such a role has not been suggested by the instant disclosure. The requirement for further research makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,

> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the Specification's assertions that the claimed PRO1268 antibodies have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

The Declaration of Dr. Grimaldi, filed under 37 CFR 1.132 (27 September 2004), is insufficient to overcome the rejection of Claims 1-5, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, as set forth in the last Office action (30 June 2004).

The Declaration of Dr. Ashkenazi, filed under 37 CFR 1.132 (27 September 2004), is insufficient to overcome the rejection of Claims 1-5, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action (30 June 2004).

Likewise, the Declaration of Dr. Polakis, filed under 37 CFR 1.132 (27 September 2004), is insufficient to overcome the rejection of Claims 1-5, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action because:

The declaration by Dr. Grimaldi has been fully considered but is not deemed persuasive. At paragraphs 5 and 6, the Applicant states that Taqman, PCR and Microarray technology all rely on the dogma that a change in mRNA will represent a similar change in protein, and cites several publications in which amplification of certain genes gives some cancers a growth or survival advantage (Singleton, et al, 1992, Pathol. Annu., 27.1: 165-173; Grimaldi, et al, 1989, Blood, 73(8): 2081-2085; Meeker, et al, 1990, 76(2): 285-289) and that if a gene product is over-or-under-expressed, it provides more accurate tumor classification and hence better determination of suitable therapy (paragraph 6). This argument has been fully considered but is

not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1268 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1268 nucleic acid was amplified in some lung or colon cancers and some normal tissues, to a minor degree, by about 2-fold. No mutation or translocation of PRO1268 has been associated with lung tumors or colon tumors. It is not known whether PRO1268 is expressed in other normal tissues besides normal lung or colon tissue, and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1268 is amplified in a small number of samples, and invite the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment. More importantly, however: there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not.

In the Declaration filed under 37 CFR 1.132 (27 September 2004), staff scientist Ashkenazi claims that the purpose of the experiments that measured increases in gene copy number was to identify tumor cell markers useful for cancer treatment (page 1, Declaration, 27 September 2004) and to identify cancers for which there was an absence of gene product over-expression (page 2).

The Ashkenazi declaration filed under 37 CFR § 1.132 argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would be useful. However, as discussed above, there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial.

Dr. Polakis (declaration filed under 37 CFR § 1.132, 27 September 2004) states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in control tissues and that antibodies have been developed that identify and could possibly be used to downregulate the PRO peptides. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. He characterizes the instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. Firstly, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO1268 in tumor samples as contrasted to normal tissue samples: Only gene amplification data were presented. As discussed above, and in the previous Office Action (page 5, 30 June 2004) this doubling of DNA levels in cancer tissue is probably due to a doubling of chromosome number, an event that is very common in cancerous tissues. In addition, it has not been shown that RNA or protein levels are increased in these two cancers. For these reasons, the Declaration is insufficient to overcome the rejection of

Claims 1-5 based upon 35 U.S.C. § 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels.

Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Doctors Grimaldi, Polakis and Ashkenazis' conclusions are provided in the declarations. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA Levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. See Hu et al. (2003, Journal of Proteome Research 2:405-412) as discussed above.

Applicants argue (page 10, 27 September 2004) that if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level, and cite: Ørntoft, et al (2002, Mol. Cell. Proteomics, 1: 37-45). Ørntoft, et al do present data that indicates a correlation between increased gene copy number and increased protein expression (see Table 1, for example). However, their error rates varied from 31% to 50%. Furthermore, since they knew the function of the genes for which they were staining, that error rate might be acceptable, if only that the expression assay can be combined with other functional assays, such that there would be a reason to detect those proteins. Such is not the case in the current Application. Applicants do not know the function of the PRO1268 polypeptide; indeed, the PRO1268 peptide has not been properly identified as yet. Therefore, it is not useful to detect a protein for which a function has not yet been identified, and additionally might only be overexpressed in several cancers and some normal tissues, and for which error rates of detection may be as high as 30-50%.

Applicants argue (Response, 27 September 2004, page 15) that even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of the evidence. Applicants provide evidence in the form of a publication by Hanna et al. (1999, Pathology Associates Medical Laboratories, 2 pages- attached to the Response of 27 September 2004). Applicants contend that the publication teaches that the HER-2/neu gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over- expression of the HER-2/neu gene product. Applicant argues that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna et al. supports the instant rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the PRO1268 polypeptides and claimed antibodies is not in currently available form, the asserted utility is not substantial.

***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire Later than SIX MONTHS from the mailing date of this final action.

***Advisory information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
30 November 2004

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER